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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,783	12/08/2005	Mitsuko Kosaka	64614(70904)	1080

21874 7590 08/13/2009

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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
08/13/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,783	KOSAKA, MITSUKO	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,12-14,17,18,26 and 27* is/are pending in the application.

4a) Of the above claim(s) *12-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,17-18,26-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. The amendments to claims and the specification filed on 17 April 2009 have been entered into the record and have been fully considered. Claims 8-11 have been cancelled. Claim 1 has been amended.

2. Claims 1-4, 6, 17-18 and 26-27, drawn to a method for producing tissue cells that are myocardial cells, comprising culturing iris pigment epithelial cells and obtaining pluripotent cells therefrom, are being considered in the instant application.

3. Applicant's arguments filed on 17 April 2009 have been fully considered. New grounds of objection and rejection are as follows.

Response to Amendment

Withdrawn objections and/or rejections

4. Upon consideration of amendments of independent claim 1 to recite the differentiation inducing conditions, rejection of claims under 35 USC 112, second paragraph is withdrawn.

5. Upon consideration of claim amendments of independent claim 1 to define the specific culture conditions, rejections of claims under 35 USC 112, first paragraph, scope of enablement and written description are withdrawn.

6. Upon consideration of amendments of independent claim 1, rejection of claims under 35 USC 103(a) is withdrawn.

New Rejections

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-4, 6, 17-18 and 26-27, are rejected under 35 U.S.C. 103(a) as being unpatentable over Kosaka et al. (Exp Cell Res 245: 245-251, 1998), and Tropepe et al. (Sc. 287: 2032-2036, 2000), in view of Pardo et al. (Brain Res 818: 84-95, 1999), and further in view of Lee et al (Theriogenology 44: 71-83, 1995) and Samarut et al., (US Patent number 6,500,668, dated 31 December 2002), as evidenced by Reynolds et al. (Sc. 255: 1707-1710, 1992) and Kitchens et al. (J. Neurobiol 25: 797-807, 1994).

9. The claims are drawn to a method for producing myocardial tissue cells comprising: (i) obtaining iris pigment epithelial cells and dissociating the isolated cells; (ii) culturing epithelial cells by floated coagulated mass in serum free media with N2 supplement and obtaining pluripotent stem cells (claim 1-3), wherein the stem cells are Oct-3/4 positive (claim 4); (iii) obtaining myocardial cells from the

pluripotent stem cells by culturing the cells in avian and fetal calf serum containing media, wherein the medium also contains a growth factor (FGF2 and EGF). The claims further recite the extirpation of iris tissue by excising the tissue from the eyeball of an animal, treating with enzyme (dispase and EDTA) and restoring the tissue in medium containing fetal calf serum (claim 6, 26-27). Furthermore, the claims recite testing for a myocardial cell specific gene, for example myosin (claims 17, 18).

10. Kosaka et al. teach the removal of eyeballs from 1 day old (postnatal) chicken, followed by incision around the iris, incubating the tissue in dispase solution and thereafter in EDTA (page 246, col 1, para 3), mechanically isolating the pigmented epithelial cells from the iris so as to prevent contamination with the other cell types, and culture in Eagle's MEM (EMEM) medium containing fetal bovine serum. Isolated pigmented epithelia are thereafter dissociated into a single cell suspension after treatment with 0.1% trypsin in PBS (page 246, column 1, "Preparation of cell"). Kosaka et al. further teach the growth of the iris derived pigmented epithelial cells in culture for 18 days before reaching confluency. The depigmented iris pigment epithelial cells are harvested and cultured for transdifferentiation to lens tissue using EMEM medium with serum and FGF (page 246, column 1, "Procedure for cell culture"; page 248, col 1, para 2).

11. Kosaka et al. do not teach the culturing of iris pigment epithelium cells by floated coagulated mass culturing technique.

12. Tropepe et al. teach the proliferation of pigmented cells from the ciliary margin (PCM) obtained from adult mouse eyes using the in vitro spherical colony forming culture method. Specifically, Tropepe et al. teach the formation of free-floating PCM spheres using the "neurosphere" formation culture method of Reynolds et al (see cross-reference 6, 8; page 2032, col 2) comprising culturing in serum-free culture medium supplemented with a defined hormone and salt mixture (comprising insulin, transferrin, progesterone, putrescine and selenium salt). Although the reference does not mention N2 supplement, the ingredients of the salt mixture presented in parenthesis above correspond to N2 supplement (see N2 Product Description Sheet from Stem Cell technologies). Furthermore, Tropepe et al teach that the coagulated mass culture results in PCM stem cells that are multipotential (page 2034, col 1, para 2).

13. Kosaka et al. and Tropepe et al. do not teach rotation of the IPE cells in culture medium during the floated coagulated mass culturing technique. Kosaka et al and Tropepe et al. also do not teach the addition or EGF and avian serum in the culture medium.

14. Pardo et al. teach aggregating brain cell cultures as a useful in vitro model for brain ischemia. The reference teaches that cell aggregates in culture can be mediated by rotation to form even-sized spherical structures comprising neuronal cells (abstract, Introduction), similar to coagulated cell mass of the instant claims.

15. Lee et al. teach that the addition of FGF and EGF have a synergistic effect on increasing the number of blastocysts and the development of embryo in vitro (abstract).

16. Samarut et al. teach the culture of bird embryonic stem cells using a culture medium comprising fetal bovine serum and chicken (or avian serum) (claims 1, 2).

17. Although the references do not explicitly teach the expression of Oct3/4, this limitation is not intended as part of the claimed method, rather is intended to recite a characteristic of the claimed pluripotent stem cells. Additionally, since the cells of Kosaka et al. are derived from the same source as the instant application, are cultured under similar differentiation conditions, as taught by the combined references of Kosaka et al, Lee et al. and Samarut et al., and use the floated coagulated mass culture of Tropepe et al. producing multipotential cells, the teachings of the combined references as explained above inherently describe cells having the same differentiation properties, and would be expected to express the same markers. That the references are silent on the expression of the cardiac marker genes does not provide proof of the cell being different, particularly if the other conditions (as stated above) are satisfied.

18. It would have been, therefore, obvious to the person of ordinary skill in the art at the time the claimed invention was made to modify the method of isolating and culturing the iris pigment epithelial cells of Kosaka et al. and Pardo et al. in culture conditions comprising avian serum and FBS along with growth factors

EGF and FGF in view of Lee et al and Samarut et al, to the floated coagulated mass culture technique as taught by Tropepe et al. The person of ordinary skill in the art would have been motivated to use the floated coagulated mass culture technique for cell culture and differentiation as this would produce multipotent (or pluripotent) cells demonstrating various lineages (Tropepe et al., page 2034, col 1, para 2). Furthermore, as evidenced by Reynolds et al., the method would facilitate the selection of a specific cell type aggregate by antibody immuno-staining (page 708, Figure 1E and 1F). Moreover, it is well established that stem cell culture require a high concentration of serum, and chick serum would additionally provide growth factors for the survival of chicken iris cells. Also established is the fact that both FGF and EGF are mitogens required for growth and differentiation of cells, as evidenced by Kitchens et al (abstract). The person of ordinary skill in the art would have expected success because the method of floated coagulated mass technique involving various tissues, was well established and accepted in the art at the time the invention was made.

19. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Applicant's Response

20. Applicant's arguments directed to the 103 rejection (over the combined references of Kosaka et al., Torpepe et al. and Reynolds et al.) of the previous Office Action, are considered moot as the rejection has been withdrawn (see

para 5 of the instant action). However, Applicant's comments traversing the rejection based on lack of teachings of the differentiation inducing conditions in the cited references will be addressed below.

21. Applicant has largely based the arguments over the newly introduced limitations reciting specific differentiation conditions. Applicant asserts that the cited references do not disclose these conditions and therefore, the instant invention is not obvious in view of the references. Additionally, Applicant argues that the amended claims recite a "unique effect" such that the myocardial cells can be obtained from pluripotent cells derived from IPE cells by floated coagulated mass culture technique. Applicant alleges that the combination of the references could only be made in hindsight, thus the teaching of these references cannot provide "a finite number of predictable solutions" and further asserts that no specific market pressure has been identified. Furthermore, Applicant argues that Kosaka's teaching indicates that culture conditions of one cell type are different from that of the other. For example, the differentiation conditions required for RPE is not the same as that required for IPE, therefore, it would not be obvious for a skilled person to modify Kosaka and look to the Tropepe teaching directed to the culture of PCM cells. Applicant further asserts that the skilled artisan would not look to teachings using Tropepe medium after using serum containing medium as taught by Kosaka. Lastly Applicant argues that since Pardo does not teach transdifferentiation or differentiation, Pardo does not provide a motivation for modifying Kosaka or Tropepe. Applicant emphatically

reminds that the claimed method first requires serum free medium, thereafter serum containing medium, which is not attained by combining the references, thus requests that the rejection should be withdrawn.

22. Applicant's arguments are fully considered, however, are not found to be persuasive. A prima facie case of obviousness was correctly established, because the combined references taught the use of serum as recited in the method steps. The claims are drawn to a method comprising obtaining iris pigment epithelial cells from the eyeball of an animal and dissociating the isolated cells by treating with enzyme (dispase and EDTA) and restoring the tissue in **medium containing serum**; culturing epithelial cells by floated coagulated mass in **serum free media with N2 supplement** and obtaining pluripotent stem cells; obtaining myocardial cells by differentiation from the pluripotent stem cells by culturing the cells in **serum containing media** and growth factor/factors. It is noted that the isolation and tissue restoration is done using medium containing serum (Kosaka and Samarut). Kosaka is also teaching the transdifferentiation of IPE in serum containing medium, which is what the claimed method recites. Kosaka is not teaching the floated coagulated mass culture technique. Tropepe teaches this method in serum free medium containing the N2 supplement, for selective culturing and differentiation to various cell types. As stated above, it is reiterated that the person of ordinary skill in the art would have been motivated to modify the method of differentiation by using the floated coagulated mass culture technique for cell culture and differentiation as this

would produce pluripotent cells demonstrating various lineages by selecting a specific cell type aggregate by immuno-staining, for example. Applicant's arguments on page 9, last paragraph, reasoning the inability to use Tropepe method using serum free medium plus the various molecules after using serum containing medium (Kosaka teaching) is inconsistent, especially in view of the steps recited in the claimed method.

23. Additionally, Applicant is arguing subject matter from the reference that is not relevant to the claimed invention. Applicant is arguing limitations that are not present or required in the current claims. For example the differences in cell types IPE versus RPE, and the selection of culture medium to deal with the differences, is not relevant to the instant claim invention, particularly when the combined teachings clearly render the claimed invention obvious to the skilled artisan. Furthermore, it is a known fact that different cell types require different culture conditions. It is reiterated that the teachings in the cited art rely on the same source as the instant invention and provides a highly reproducible process for preparing a homogenous cell population, “thereby providing a tool for biochemical and biological molecule analyses” (Kosaka, page 249, col 1, para 1). Based on the above discussion, the claimed invention would be prima facie obvious to the skilled artisan over the combined teachings of the prior art. Applicant is reminded that “one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck*

& Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). "The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference.... Rather, the test is what the combined teachings of those references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). See also *In re Sneed*, 710 F.2d 1544, 1550, 218 USPQ 385, 389 (Fed. Cir. 1983).

24. Furthermore, Applicants may argue that the examiner's conclusion of obviousness is based on improper hindsight reasoning. However, "[a]ny judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." *In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971). Applicants may also argue that the combination of two or more references is "hindsight" because "express" motivation to combine the references is lacking. However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). **>See MPEP § **2141** and § **2143** for guidance regarding establishment of a *prima facie* case of obviousness.

25. Lastly, the combination of the above references proves that the knowledge and expertise for the claimed method for selective culturing and differentiating pluripotent stem cells to various lineages and producing tissue cells from IPE cells was known in the art and the results were expected to be successful. The prima facie obviousness of the claimed invention in view of the combined references, therefore, provides sufficient reasoning, and nullifies Applicant's allegations of the improper teachings in the individual references. Applicant's assertion of a "unique effect" to produce myocardial cells does not overcome the rejection because of obvious expected properties taught in the prior art, either explicitly or implicitly. "Where the unexpected properties of a claimed invention are not shown to have a significance equal to or greater than the expected properties, the evidence of unexpected properties may not be sufficient to rebut the evidence of obviousness". *In re Nolan*, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (CCPA 1977).

Conclusion

26. No claims are allowed.

27. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

28. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

31. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-

direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
6 August 2009

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649